FATENT COOPERATION TREAFY

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| PCT | То: |
| NOTIFICATION OF ELECTION (PCT Rule 61.2) | United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ETATS-UNIS D'AMERIQUE |
| Date of mailing (day/month/year) 09 June 1998 (09.06.98) | in its capacity as elected Office |
| International application No. PCT/GB97/02907 | Applicant's or agent's file reference N.71868A GCW |
| International filing date (day/month/year) 21 October 1997 (21.10.97) | Priority date (day/month/year) 21 October 1996 (21.10.96) |
| Applicant | |
| WRIGLEY, Stephen, Keith et al | |
| The designated Office is hereby notified of its election made in the demand filed with the International Preliminar 18 May 1998 (in a notice effecting later election filed with the International Preliminar 18 May 1998 (in a notice effecting later election filed with the International Preliminar 19 May 1998 (in a notice effecting later election filed with the International Preliminar 19 May 1998 (in a notice effecting later election filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminar 19 May 1998 (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed with the International Preliminary (in the demand filed w | y Examining Authority on: 18.05.98) |
| 2. The election X was was not was not made before the expiration of 19 months from the priority Rule 32.2(b). | date or, where Rule 32 applies, within the time limit under |

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38



PATENT COOPERATION TREATY

1 3 OCT 1998 REC'D POT WIPO

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

| | | (PCT Article 36 and | | <u> </u> |
|-------------------|---|---|--------------------------|---|
| • • | agent's file reference | FOR FURTHER ACTION | See Pre | Notification of Transmittal of International liminary Examination Report (PCT/IPEA/416) |
| 1.71868A (| | International filing date (day/month/y | ro ar l | Priority date (day/month/year) |
| | | | ear) | 21/10/1996 |
| PCT/GB97/ | | | | 21/10/1000 |
| | | or national classification and IPC | | |
| CO7D309/3 | 2 | | | |
| | | | | |
| Applicant | | | | |
| KENOVA L | IMITED et al. | | | |
| | | | | At we still a st Destination of Everying Author |
| 1. This into | ernational preliminary e cansmitted to the applic | xamination report has been prepared ant according to Article 36. | by this in | ternational Preliminary Examining Auth |
| and is ti | anomitted to the applie | <u></u> | | |
| 2. This RE | PORT consists of a tot | al of 4 sheets, including this cover s | heet. | ` |
| | | | | d de descripto |
| ⊠ Th | is report is also accomp | panied by ANNEXES, i.e., sheets of t ed and are the basis for this report an | he descrip d/or sheet | otion, claims and/or drawings is containing rectifications made |
| be | fore this Authority (see | Rule 70.16 and Section 607 of the A | dministrat | ive Instructions under the PCT). |
| | | | | |
| These a | annexes consist of a to | tal of 1 sheets. | | |
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| 3 This rea | oort contains indication | s relating to the following items: | | |
| 0. ,,,,,,,,,, | | | | |
| l | Basis of the reperior Basis of the | ort | | |
| II. | ☐ Priority | | | |
| III | ☐ Non-establishm | ent of opinion with regard to novelty, | inventive | step and industrial applicability |
| IV | Lack of unity of | | | |
| V | Reasoned state citations and ex | ment under Article 35(2) with regard planations supporting such statemen | to novelty t | , inventive step or industrial applicability; |
| VI | ☐ Certain docume | ents cited | | |
| VII | □ Certain defects | in the international application | | |
| VIII | ☐ Certain observa | ations on the international application | | |
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| | | | 4 | a of this coppet |
| Date of sub | mission of the demand | Date o | r completio | n of this report |
| 10/05/1000 | | | | 0 9. 10. 98 |
| 18/05/199 | 1 5 | | | |
| Name and r | nailing address of the IPE | A/ Autho | ized office | SPISORS M. |
| | European Batant Office | | | (S |
| 16. | European Patent Office D-80298 Munich | Bole | ti-Creme | rs, K 🐚 💯 |
| <i> <u> </u></i> | Tel. (+49-89) 2399-0, T | | | 40.80) 2399-8541 |

Telephone No. (+49-89) 2399-8541

Fax: (+49-89) 2399-4465

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/GB97/02907

| Basis of the report | t |
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| 1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving response to an invitation under Article 14 are referred to in this report as "originally filed" and are not anneathe report since they do not contain amendments.): |
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| 1. | resp | report has been d conse to an invitation report since they d | on unde | er Article | 9 14 are r | eferred | sneets wnich to in this repo | nave been lun rt as "originally | filed" and are not annexed | d to |
|----|--------------|--|-------------------|-----------------------|---------------------------|--------------------------|---------------------------------|------------------------------------|----------------------------|------|
| | Des | cription, pages: | | | | | | | | |
| | 1-29 |) | as orig | ginally fi | led | | | | | |
| | Clai | ms, No.: | | | | | | | | |
| | 1-7, 14-1 | 8 (part),13 (part), I7 | as oriç | ginally f | iled | | | | | |
| | ••• | art),9-12, part) | as rec | eived o | n | | 29/09/1998 | with letter of | 28/09/1998 | |
| 2. | The | amendments hav | e result | ed in th | e cancell | ation of: | | | | |
| | | the description, | pag | jes: | | | | | | |
| | | the claims, | No | s.: | | | | | | |
| | | the drawings, | she | ets: | | | | | | |
| 3. | | This report has be considered to go | een est beyond | ablished I the dis | d as if (so sclosure a | ome of) t is filed (l | he amendme Rule 70.2(c)): | nts had not bee | en made, since they have l | beer |
| 4. | Add | ditional observation | ns, if ne | cessary | r: | | | | | |
| V. | Rea | asoned statemen olicability; citatio | t under ns and | Article explan | 35(2) wi ations su | ith rega upportin | rd to novelty ng such state | , inventive ste ment | p or industrial | |
| 1. | Sta | tement | | | | | | ٠ | | |
| | No | velty (N) | | Yes: No: | Claims Claims | 1-13 | | | | |
| | Inv | entive step (IS) | | Yes: No: | Claims Claims | 1-13 | | | | |
| | Ind | lustrial applicability | / (IA) | Yes: No: | Claims Claims | 1-13 | | | | |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/02907

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

POINT V.

- 1. The following documents, quoted in the I.S.R., have been considered as relevant for the examination of the present application. Their numbering will be adhered to for the rest of the procedure.
 - (1) J.O.C., vol 58, no.25, 1993, pp.7195-7203.
 - (2) J.C.S, Perkin Transactions 1, vol.12, 1996, pp. 1385-1392.
- 2. In view of the content of documents (1) and (2) (see (1) , p. 7196 , compound 17 , see (2) , p. 1388, compound 4R) , present reformulated matter according to claim 12 can now be regarded as novel, because both documents disclose the originally claimed fatty acid of formula III b where R¹ and R² are H, prepared otherwise as in the present application. The content of (1) and (2) being deleted from the original claimed matter according to claim 12, novelty is acknowledged. Since both (1) and (2) do not refer to the the preparation of the pyrones (I) of the present application , the remaining claims can be considered as novel and inventive in the light of said documents.

POINT VII.

- (1) The decription should be amended to correpond to the present reformulated matter (see especially p.7 of the description).
- (2) Documents (1) and (2) should be named in the description and briefly discussed.

INTERNATIONAL SEARCH REPORT

Inte hal Application No PCT/GB 97/02907

| IPC 6 | FICATION OF SUBJECT MATTER C07D309/32 C12P7/40 C12P17/0 C12N1/14 //(C12N1/14,C12R1:649 | | 7C57/03 | | | | |
|---|--|---|---------------------------|--|--|--|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | | | | | | |
| B. FIELDS | SEARCHED | | | | | | |
| Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D C12P C07C | | | | | | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) | | | | | | | |
| | | | | | | | |
| С. БОСИМ | ENTS CONSIDERED TO BE RELEVANT | | | | | | |
| Categon: | Citation of document, with indication, where appropriate, of the rele | evant passages | Relevant to claim No. | | | | |
| А | P.WIPF ET AL.: "TOTAL SYNTHESEIS STRUCTURE ASSIGNMENT OF THE ANTII ARANOROSIN." JOURNAL OF ORGANIC CHEMISTRY., vol. 58, no. 25, 1993, EASTON to pages 7195-7203, XP002052631 see page 7195, paragraph EXPERIM. 7196 | TUMOR JS, | 1,12 | | | | |
| X | A.MCKILLOP: "THE TOTAL SYNTHESIS DIEPOXYCYCLOHEXANONEANTIBIOTIC AF JOURNAL OF THE CHEMICAL SOCIETY, TRANSACTIONS 1., vol. 12, 21 June 1996, LETCHWORTH pages 1385-1392, XP002052632 see page 1385, paragraph EXPERIM | RANOROSIN" PERKIN | 12 | | | | |
| Funt | ner documents are listed in the continuation of box C. | Patent family members are list | ted in annex. | | | | |
| ' Special ca | tegories of cited documents : | "T" later document published after the | international filing date | | | | |
| "A" document defining the general state of the art which is not cited to understand the principle or theory underlying the | | | | | | | |
| considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention | | | | | | | |
| filing date cannot be considered novel or cannot be considered to "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "V" document of particular relevance; the claimed invention involve an inventive step when the document is taken alone which is cited to establish the publication date of another | | | | | | | |
| "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document referring to an oral disclosure, use, exhibition or | | | | | | | |
| other means ments, such combination being obvious to a person skilled in the art. | | | | | | | |
| later than the priority date claimed "&" document member of the same patent family | | | | | | | |
| | actual completion of the international search O January 1998 | Date of mailing of the international 04/02/1998 | эваны героп | | | | |
| Name and | nailing address of the ISA | Authorized officer | | | | | |
| und n | European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk | Authorized officer | | | | | |
| | Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 | Francois, J | | | | | |



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

C07D 309/32, C12P 7/40, 17/06, C07C 59/42, 57/03, C12N 1/14 // (C12N 1/14, C12R 1:645, 1:79)

(11) International Publication Number:

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30 April 1998 (30.04.98)

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21 October 1996 (21.10.96)

GB (

(71) Applicant (for all designated States except US): XENOVA LIMITED [GB/GB]; 240 Bath Road, Slough, Berkshire SL1 4EF (GB).

(72) Inventors; and

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SON, Neil [GB/GB]; 240 Bath Road, Slough, Berkshire SL1 4EF (GB). HAYES, Martin, Alistair [GB/GB]; 240 Bath Road, Slough, Berkshire SL1 4EF (GB). MANDER, Thomas, Haydn [GB/GB]; 240 Bath Road, Slough, Berkshire SL1 4EF (GB).

- (74) Agents: KEEN, Celia, Mary et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).
- (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: CYTOKINE PRODUCTION INHIBITORS

(57) Abstract

A 5,6-dihydro- α -pyrone of formula (I) wherein R is CO2H or CH3 and each of R1 and R² is H; or R is CO₂H, one of R1 and R2 is H and the other is OH; or when R is CO₂H, a pharmaceutically veterinarily acceptable Processes for salt thereof. producing compounds of formula (I) and their use as cytokine production inhibitors are also described.

FOR THE PURPOSES OF INFORMATION ONLY

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| EE | Estonia | LR | Liberia | SG | Singapore | | |

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | | of Transmittal of International Search Report | | | | | |
|---|---|---|--|--|--|--|--|
| N.71868A GCW | ACTION | 220) as well as, where applicable, item 5 below. | | | | | |
| International application No. | International filing date (day/month/year) | (Earliest) Priority Date (day/month/year) | | | | | |
| PCT/GB 97/02907 21/10/1997 21/10/1996 | | | | | | | |
| Applicant | | | | | | | |
| XENOVA LIMITED et al. | | | | | | | |
| This International Search Report has be according to Article 18. A copy is being to | en prepared by this International Searching Aut ransmitted to the International Bureau. | hority and is transmitted to the applicant | | | | | |
| This International Search Report consist | s of a total of <u>2</u> sheets. py of each prior art document cited in this report | t. | | | | | |
| Certain claims were found ui | nsearchable (see Box I). | | | | | | |
| 2. Unity of invention is lacking | (see Box II). | | | | | | |
| international search was carrie | ontains disclosure of a nucleotide and/or amin d out on the basis of the sequence listing ed with the international application. Inished by the applicant separately from the inte | | | | | | |
| 101 | but not accompanied by a statement to it matter going beyond the disclosure in the | he effect that it did not include | | | | | |
| Tra | anscribed by this Authority | | | | | | |
| 4. With regard to the title , \(\chi\) the | e text is approved as submitted by the applicant | | | | | | |
| the | e text has been established by this Authority to r | read as follows: | | | | | |
| | | | | | | | |
| 5. With regard to the abstract, | e text is approved as submitted by the applicant | | | | | | |
| the Bo | e text has been established, according to Rule 3 ox III. The applicant may, within one month from arch Report, submit comments to this Authority | 88.2(b), by this Authority as it appears in the date of mailing of this International | | | | | |
| 6. The figure of the drawings to be put | plished with the abstract is: | | | | | | |
| Figure No as | suggested by the applicant. | None of the figures. | | | | | |
| be | cause the applicant failed to suggest a figure. | | | | | | |
| be | cause this figure better characterizes the invent | tion. | | | | | |

INTERMATIONAL SEARCH REPORT

tional Application No PC1/GB 97/02907

| A. CLASSI IPC 6 | FICATION OF SUBJECT MATTER C07D309/32 C12P7/40 C12P17/0 C12N1/14 //(C12N1/14,C12R1:645 | 06 C07C59/42 C0 5,C12R1:79) | 07C57/03 | | | |
|--|---|---|---------------------------------------|--|--|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | | | | | |
| | SEARCHED | | · · · · · · · · · · · · · · · · · · · | | | |
| IPC 6 | ocumentation searched (classification system followed by classification CO7D C12P C07C | n symbols) | | | | |
| Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched | | | | | | |
| Electronic d | data base consulted during the international search (name of data bas | se and, where practical, search terms | used) | | | |
| C. DOCUM | ENTS CONSIDERED TO BE RELEVANT | | | | | |
| Category ° | Citation of document, with indication, where appropriate, of the rele | vant passages | Relevant to claim No. | | | |
| A | P.WIPF ET AL.: "TOTAL SYNTHESEIS STRUCTURE ASSIGNMENT OF THE ANTIT ARANOROSIN." JOURNAL OF ORGANIC CHEMISTRY., vol. 58, no. 25, 1993, EASTON L pages 7195-7203, XP002052631 see page 7195, paragraph EXPERIM. 7196 | TUMOR US, | 1,12 | | | |
| X | A.MCKILLOP: "THE TOTAL SYNTHESIS DIEPOXYCYCLOHEXANONEANTIBIOTIC AR JOURNAL OF THE CHEMICAL SOCIETY, TRANSACTIONS 1., vol. 12, 21 June 1996, LETCHWORTH pages 1385-1392, XP002052632 see page 1385, paragraph EXPERIM | RANOROSIN" PERKIN | | | | |
| Furt | her documents are listed in the continuation of box C. | Patent family members are li | sted in annex. | | | |
| "A" docume consic "E" earlier of filing of "L" docume which citatio "O" docum other "P" docum later ti | ent which may throw doubts on priority claim(s) or is cited to establish the publicationdate of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but han the priority date claimed | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family | | | | |
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| | 0 January 1998 | 04/02/1998 | 04/02/1998 | | | |
| Name and r | mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016 | Authorized officer Francois, J | | | | |

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